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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

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12/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,328	HANNAH ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,49-51 and 53-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,49-51 and 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/2009 and 11/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 8/27/2009, are acknowledged and entered. Claims 1-38, 49-51, and 53-58 are pending and under examination.

Response to Arguments

Applicants' arguments, filed 8/27/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 8/27/2009 and 11/23/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 and 53-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of

Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a subject an amount of a compound recited in claim 1, 9, 36, or 53 to provide a maximum concentration of 20 to 4000 mg/mL of the compound in the subject's plasma or 40 to 8000 mg/mL of the compound in the subject's blood (claims 1 and 53), 10 to 2,000 ng/mL of the compound in the subject's plasma 24 hours after administration or 20 to 4,000 ng/mL of the compound in the subject's blood 24 hours after administration (claim 9, an AUC of 500 to 60,000 mg*h/mL of the compound in the subject's plasma or 750 to 120,000 ng*h/mL of the compound in the subject's blood (claim 36).

The claims thus recite functional limitations regarding the amount of compound to be administered to a subject wherein the amount of compound administered is "to provide" a particular C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration. At the time the invention was made, Applicants were not in possession of such amounts of administered compound, other than the amounts administered by a particular administration route and administration regimen as disclosed in Table 5 (*i.e.*, 3, 10, 30, 100, 200, or 300 mg/kg/day orally administered once daily).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to administration of the claimed compounds in amounts "to provide" a particular Cmax range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration. The skilled artisan would recognize that different amounts of administered compound, administration routes, and administration regimens (e.g., once daily administration, once weekly administration, etc.) all have a profound effect on the pharmacokinetics of a particular pharmaceutical agents. As such, other than oral administration of the compound recited in claims 1, 9, and 36 once daily at doses of 3, 10, 30, 100, 200, and 300 mg/kg/day, Applicants have not described amounts, administration routes, and administration regimens that would result in the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration.

While it is acknowledged that Applicants disclose that the compound of the invention can be administered by injection as a short bolus, slow infusion, or long-term infusion (page 7, [0016]) in amounts ranging from 0.25 to 30 mg/kg body weight or 25 to 1500 mg/day (page 7, [0017]) and that the compound can be administered in a treatment cycle comprising administering the compound daily for 7, 14, 21, or 28 days followed by 7 or 14 days without administration of the compound (page 7, [0019]), the fact remains that the specification only provides written support for once daily oral administration at doses of 3, 10, 30, 100, 200, and 300 mg/kg/day to provide the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration.

Determination of other administration routes, dosing regimens, and amounts of the claimed compounds that would result in the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration would require random hit-or-miss testing of different combinations of administration routes, dosing regimens, and amounts of the claimed compounds (*e.g.*, twice daily infusion of 10 mg/kg over 3 hours every 5 days, oral administration of 5 mg/kg three times per day for 5 days, once daily infusion of 5 mg/kg over 12 hours every other day, etc.). The fact that such testing is routine does not negate the fact that Applicants have not adequately described such administration routes, dosing regimens, and amounts of the claimed compounds that will lead to the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration.

Accordingly, in the absence of sufficient recitation of distinguishing characteristics (*e.g.*, dose, administration route, administration regimen), the specification does not provide adequate written description of the claimed "amount" of the disclosed compound "to provide" the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration, and purported to have anticancer activity. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the broadly claimed amounts (which necessarily include particular administration routes and administration regimens) of the disclosed compounds. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9-13, 17, 19-30, 35-38, 49, and 53-58 are rejected under 35 U.S.C. 103(a) as being obvious over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **Glade-Bender *et al.*** (Expert Opin. Biol. Ther., April 2003, vol. 3, no. 2, pages 263-276) (newly cited) and **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18).

The applied reference (Renhowe *et al.*) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective

U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims recite methods of treating cancers selected from the group consisting of gastrointestinal stromal cancer, glioma, melanoma, bladder cancer, and renal cancer comprising comprising administering 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one in amounts to provide ranges of C_{max}, ng/mL, and AUC values as recited in the instant claims.

Renhowe *et al.* teach a genus of compounds that are small molecule inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinases for treating diseases characterized by angiogenesis, including cancer (col. 1, lines 11-21). Members of the VEGF subfamily of receptor tyrosine kinases are taught to induce vascular permeability and endothelial cell proliferation and to induce angiogenesis and vasculogenesis (col. 2, lines 13-16).

Accordingly, the inventors sought to develop compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, and/or inhibit vascular endothelial growth factor receptor tyrosine kinase (col. 3, lines 27-35). To this end, the inventors teach a genus of quinolinone compounds (col. 3, line 39 to col. 18, line 21), of which the instantly claimed compound is a specie and is explicitly recited as Example 109 at column 86, lines 64-66 and column 97, lines 23-24. This compound, along with a series of other compounds, is to have an IC_{50} value of less than 10 μM with respect to VEGFR1, VEGFR2, and bFGF (col. 101, lines 45-47).

With regard to claims 17 and 19-22, the compounds disclosed in Renhowe *et al.* may be formulated in pharmaceutical compositions comprising pharmaceutically acceptable carriers, excipients, binders, diluents, and the like (col. 57, lines 62-66) as well as thickeners, buffers, sweeteners, and flavoring agents (col. 59, line 1). Liquid dosage forms comprising water as recited in claim 19 are disclosed at column 59, lines 5-14, lines 37-47, and lines 48-59.

With regard to claim 23, the compounds of the invention may be formulated in compositions for various routes of administration (col. 57, line 62 to col. 60, lines 32), such as in injectable dosage forms (col. 59, lines 37-59).

With regard to claims 24 and 35, specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40). As such, administration of the compounds of Renhowe *et al.* necessarily include at least administration once a day as recited to claims 24 and 35.

With regard to claims 25-27, which recite doses of 0.25 to 30 mg/kg body weight (claim 25), 25 to 1500 mg/day (claim 26), and 200 to 500 mg/day (claim 27), Renhowe *et al.* do not explicitly disclose the amounts of the disclosed compounds. However, Renhowe *et al.* do teach that the compounds of their invention are administered in an "effective amount" and that specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). As such, the claimed doses are not seen as being a patentable distinction over Renhowe *et al.* who teach, suggest, and motivate the administration of compounds of their invention in an effective amount to treat the disclosed conditions. One skilled in the art at the time the invention was made would have been motivated to determine optimal doses of the claimed compound for administration to a subject having cancer as suggested and motivated by the teachings of Renhowe *et al.*

With regard to "treating", the inventors teach that this means, for example, within the context of treating patients in need of an inhibitor of VEGF-RTK, a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells (col. 60, lines 52-63).

With regard to claims 57 and 58, which recite metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one, the administration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient as suggested and motivated by Renhowe *et al.* will necessarily result in the "administration" of the metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as recited in the instant claims because such metabolites are formed, by definition, by the action of enzymes in the body of a patient administered 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

Glade-Bender *et al.* provide a review of VEGF blocking therapy in the treatment of cancer. In this regard, VEGF is disclosed as the "best-characterized" pro-angiogenic factor that is "virtually ubiquitous" in human tumors, wherein higher levels of VEGF have been correlated with more aggressive disease (Abstract). The authors teach that effective blockade of the VEGF pathway has been demonstrated with multiple agents, including receptor tyrosine kinase inhibitors (id.). Regarding cancer types which have been successfully treated with small molecule inhibitors of VEGF, such cancer types include melanoma and glioma (page 268, paragraph bridging left and right columns) and renal cancer (page 269, right column). Small molecule inhibitors of VEGF have been administered by twice-weekly infusions in doses ranging from 4.4 to 190 mg/m^2, a five day load of 20 mg/m^2/day followed by weekly infusion of 65-190 mg/m^2, 1-3 times daily oral administration in 28-day cycles, and 50-2000 mg/m^2 once-daily (page 268, right column; page 269, left and right columns).

While Renhowe *et al.* do not disclose that administration of the compounds of their invention, including the claimed compound, provide the C_{max}, ng/mL in plasma or blood, or AUC values recited in the instant claims, in the absence of evidence to the contrary administration of an "effective amount" of the compounds of Renhowe *et al.* to treat cancer will necessarily result in the claimed C_{max}, ng/mL in plasma or blood, and AUC values recited in the instant claims. Applicant's characterization of the pharmacokinetics of administration of the claimed compound is not seen as a patentable distinction over the administration of an "effective amount" as disclosed in Renhowe *et al.* Further, the FDA guidelines for the format and content of the human pharmacokinetic and bioavailability section of a New Drug Application teaches that biopharmaceutic studies are required by the Food, Drug, and Cosmetic Act (page 1). Such

studies include pharmacokinetic studies assessing the time course of drug and major metabolite concentrations in blood and other body compartments (pages 3-4). The studies provided in support of a New Drug Application, the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes (page 4). Pharmacokinetic parameters should include C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from each *in vivo* study (page 6).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a therapeutically effective amount of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient in need thereof (*e.g.*, a patient having a cancer or tumor). In support of the obviousness of the claimed methods, the Examiner makes the following findings of fact:

(i) The instantly claimed compound and related compounds were known in the art and were known to inhibit at least VEGFR1, VEGFR2, and bFGF;

(ii) Inhibition of such receptor tyrosine kinases was suggested by the prior art to be useful in the treatment of cancers;

(iii) Therapeutically effective amounts of the claimed compound are suggested by the prior art to vary depending on the route of administration and dosage form;

(iv) melanoma, glioma, and renal cancer have all been effectively treated with small molecule inhibitors of VEGF; and

(v) Measuring pharmacokinetic parameters such as C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from *in vivo* studies is a requirement before a new drug can be approved for use in human patients.

Thus, Renhowe *et al.* provide explicit teaching, suggestion, and motivation to administer the instantly claimed compound and structurally related compounds to patients in need thereof, which patients include those having a cancer or tumor with expressing a vascular endothelial growth factor receptor tyrosine kinase. As evidenced by Glade-Bender et al., gliomas, melanomas, and renal cancer are all effectively treated with small molecule inhibitors of VEGF, thus providing the skilled artisan with the motivation to use the VEGF inhibitors disclosed in Renhowe et al. to treat these cancers.

The skilled artisan would have been motivated to administer the claimed compound to treat a cancer expressing VEGF as suggested by the teachings of Renhowe *et al.* In view of the teachings of Glade-Bender *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that administration of a compound disclosed in Renhowe *et al.* would be effective to treat glioma, melanoma, and renal cancer because these cancers have all been effectively treated with small molecule inhibitors of VEGF.

With respect to the claimed pharmacokinetic values, Applicants have presented no evidence that administration of an effective amount of a compound disclosed in Renhowe *et al.*, including the instantly claimed compound, to treat cancer in a patient does not result in the Cmax, ng/mL in blood or plasma, or AUC ranges recited in the instant claims. As such, in the absence of such evidence, it is the position of the Examiner that administration of the claimed compound to treat cancer in a subject as suggested and motivated by the teachings of Renhowe *et al.* and Glade-Bender *et al.* necessarily meets these claim limitations. In other words, Applicants' characterization of the pharmacokinetics of the claimed compounds is not a patentable distinction over the cited prior art.

Response to Arguments

To the extent that Applicants' arguments pertain to the new ground of rejection discussed supra, the Examiner will address Applicants' arguments herein.

Applicants argue that none of the cited references teaches the use of the present compounds at the present blood levels for the treatment of the claimed cancers and that the Office has not explained why the skilled artisan "would modify the prior art methods" with a reasonable expectation of success to treat the cancers recited in the present claims. As a first matter, newly cited Glade-Bender et al. teach that cancers recited in the instant claims (i.e., glioma, melanoma, and renal cancer) have been effectively treated with inhibitors of VEGF. As such, the skilled artisan would expect that the inhibitors of VEGF disclosed in Renhowe et al. would also be effective to treat these cancers. Secondly, regarding the claimed blood levels of the present compounds, it is the position of the Examiner that no "modification" of the prior art methods are necessary to meet these limitations. Renhowe et al. teach, suggest, and motivate administering the disclosed compounds to treat cancer in "effective amounts". Applicants have

presented no factual evidence that amounts of the claimed compounds effective to inhibit VEGF in a subject and treat cancer in a subject are not amounts that do not result in the claimed blood levels of the compound. Furthermore, as discussed supra, determining the pharmacokinetics of a therapeutic compound is routine in the art and is in fact required by the FDA. As such, choosing a VEGF inhibitor compound from those disclosed in Renhowe et al., determining effective amounts of said compound to treat cancer (as suggested and motivated by Renhowe et al.), and measuring the pharmacokinetics of the compound would have been prima facie obvious to one skilled in the art.

Claims 7-8 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **Glade-Bender *et al.*** (Expert Opin. Biol. Ther., April 2003, vol. 3, no. 2, pages 263-276) (newly cited) and **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"**, as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, and 53-58 above, and further in view of **Berge *et al.*** (J. Pharm. Sci., 1977, vol. 66, no. 1, pages 1-19).

Renhowe *et al.*, Glade-Bender *et al.*, and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 7-8, 14 and 15 differ from Renhowe *et al.* and the FDA Guidelines in the recitation of administration of the lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

However, Berge *et al.* teach that the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form (page 1, left column). In this regard, Berge *et al.* teach a list of FDA approved commercially marketed salts, including the instantly claimed lactate salt (Table 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as taught in Renhowe *et al.* as a lactate salt. It is noted that Renhowe *et al.* teach that pharmaceutically acceptable salts and tautomers of the disclosed compounds are encompassed by their invention (col. 57, lines 64-65). The skilled artisan would have been motivated to do so because Renhowe *et al.* teach that pharmaceutically acceptable

salts of the compounds of their invention may be used in compositions for treating patients and Berge *et al*. teach that lactate salts of pharmaceutical agents are suitable salts approved by the FDA. As such, the skilled artisan would have been imbued with at least a reasonable expectation that a lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one could be formed and would be useful in the methods taught, suggested, and motivated by Renhowe *et al*. (*i.e*., treatment of patients).

Claims 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al***. (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **Glade-Bender *et al***. (Expert Opin. Biol. Ther., April 2003, vol. 3, no. 2, pages 263-276) (newly cited) and **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"**, as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, and 53-58 above, and further in view of **Lindell *et al***. (US 2003/0159702 A1; Published Aug. 28, 2003; Filed Jan. 16, 2003).

Renhowe *et al*., Glade-Bender *et al*., and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 16 and 18 differ from Renhowe *et al*., Foekens *et al*., and the FDA Guidelines in the recitation of the specific sweetener, fructose, and the specific flavoring agent, mandarine.

However, Lindell *et al*. disclose that fructose is a known sweetening agent useful in pharmaceutical compositions (page 5, [0094] to page 6, [0099]) and that mandarine is a known flavoring agent (page 6, [0100]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used any known sweetener and/or flavoring agent in the formulation of a pharmaceutical composition for the administration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one. Renhowe *et al*. generally disclose that pharmaceutical compositions comprising compounds of their invention can be formulated with sweeteners and flavoring agents. As such, there is nothing unobvious or inventive about using known sweeteners and flavoring agents, such as those disclosed in Lindell *et al*., in the formulation of a pharmaceutical composition of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one for administration to a patient.

Claims 31-34 and 50-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **Glade-Bender *et al.*** (Expert Opin. Biol. Ther., April 2003, vol. 3, no. 2, pages 263-276) (newly cited) and **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"**, as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, and 53-58 above, and further in view of **Cecil Textbook of Medicine** (21st Edition, vol. 1, 2000, eds. Goldman and Bennett, pages 1060-1074).

Renhowe *et al.*, Glade-Bender *et al.*, and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 31-34 and 50-51 differ from Renhowe *et al.*, Glade-Bender *et al.*, and the FDA Guidelines in the recitation of specific dosing regimens for administration of the claimed compound. While Renhowe *et al.* suggest that specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37), the reference does not explicitly suggest the claimed treatment cycles or dosing intervals recited in claims 31-34 and 50-51.

The Cecil Textbook of Medicine discusses principles of cancer therapy, including development of a treatment plan, pharmacokinetic considerations, and dosing regimens for antineoplastic agents. With regard to pharmacokinetic considerations, the authors state that the intravenous route of a drug is preferable for most cytotoxic anticancer drugs because it ensures adequate plasma levels while minimizing compliance problems (page 1064, right column). For some agents, continuous intravenous drug administration for 4 days or longer provides better results and less toxicity that do bolus or short-duration infusions (id.). An example is provided of 5-fluorouracil which can be administered via arterial infusions for 14 days, followed by a similar rest period. As such, the claimed treatment cycle of administering the compound daily for 7, 14, 21, or 28 days, followed by 7 or 14 days without administration of the compound as recited in claim 31 would have been prima facie obvious. Pages 1065 to 1072 of Cecil discuss administration of regimens for numerous antineoplastic agents. For example, Table 198-9 at page 1071 teaches administration of drugs in the range of 20-100 mg/day, 40 mg/day for 4-day pulses every 2-4 weeks, 5 mg tid (three times a day), 1-3 mg qd (every day), 20 mg qd (every

day), 250 mg bid (twice a day), or 1 g IM biw (biweekly). Cytarabine is taught to be administered either by continuous infusion or in bolus doses by the intravenous or subcutaneous route for 5-7 days. Alternatively, cytarabine can be administered in doses of 1 to 3 grams every 12 hours for 3 to 5 days (page 1066, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used preclinical pharmacokinetic testing in order to determine the optimal treatment regimen for administration of the claimed compound to human subjects for the treatment of cancer as suggested and motivated by the combined teachings of the cited prior art. It is clear from the cited prior art that there are numerous possible administration regimens for the administration of anticancer agents. However, one skilled in the art would have been imbued with at least a reasonable expectation of success that by using known, routine methods of measuring pharmacokinetic parameters, an optimal dosing regimen for administration of the claimed compound would be attained.

In light of the teachings of Renhowe *et al.*, one skilled in the art would have been motivated to select 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one and use this compound for the treatment of cancers expressing VEGF. In developing said compound for use in the treatment of human subjects having cancer, the skilled artisan would use the FDA guidelines to determine the format and content of the human pharmacokinetic and bioavailability section of a New Drug Application, which teaches that biopharmaceutic studies are required by the Food, Drug, and Cosmetic Act (page 1). Such studies include pharmacokinetic studies assessing the time course of drug and major metabolite concentrations in blood and other body compartments (pages 3-4). The studies provided in support of a New Drug Application, the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes (page 4). Pharmacokinetic parameters should include C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from each *in vivo* study (page 6).

Following these guidelines, the skilled artisan would have been led to: (1) administer the claimed compound to subjects using different known doses, routes, and administration regimens (such as those taught in Cecil); (2) measure the pharmacokinetic parameters of the drug

following such administration; and (3) select the most efficacious and tolerable dose, administration route, and administration regimen combination. Such testing is routine in the art of the development of anticancer drugs as evidenced by Renhowe *et al.*, the FDA guidelines, and Cecil.

In light of the above discussion, the claimed treatment cycles are not seen as a patentable distinction over the cited prior art, which teaches, suggests, and motivates one skilled in the art to administer anticancer agents in different doses, via different administration routes, and using different administration cycles in order to elicit the optimal therapeutic response with minimal toxicity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 9-15, 16-38, 49-51, and 53-58 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 6,605,617 in view of **Glade-Bender *et al.*** (Expert Opin. Biol. Ther., April 2003, vol. 3, no. 2, pages 263-276). Although the conflicting claims are not identical, they are not patentably

distinct from each other because the method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase comprising administering an effective amount of a formulation comprising a compound of any of claims 1, 8, 15, or 22 as recited in claim 30 of the '617 patent encompasses the treatment of the claimed cancers using any amount of the instantly claimed compound that is "effective". As such, Applicant's characterization of the Cmax and AUC values of the instantly claimed compound is not seen as a patentable distinction over the method claimed in the '617 patent. Further, the specification of the '617 patent, when used as a dictionary to define the claimed "effective amount" states that specific dosages may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40).

Glade-Bender et al. teach that VEGF is the "best-characterized" pro-angiogenic factor that is "virtually ubiquitous" in human tumors, wherein higher levels of VEGF have been correlated with more aggressive disease (Abstract). The authors teach that effective blockade of the VEGF pathway has been demonstrated with multiple agents, including receptor tyrosine kinase inhibitors (id.). Regarding cancer types which have been successfully treated with small molecule inhibitors of VEGF, such cancer types include melanoma and glioma (page 268, paragraph bridging left and right columns) and renal cancer (page 269, right column). Small molecule inhibitors of VEGF have been administered by twice-weekly infusions in doses ranging from 4.4 to 190 mg/m^2, a five day load of 20 mg/m^2/day followed by weekly infusion of 65-190 mg/m^2, 1-3 times daily oral administration in 28-day cycles, and 50-2000 mg/m^2 once-daily (page 268, right column; page 269, left and right columns).

As such, it would have obvious to one skilled in the art that a patient with glioma, melanoma, or renal cancer is reasonably a patient "in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase" as recited in claim 30 of the '617 patent.

Claims 1-38, 49-51, and 53-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17, 34, 49, 51-52, 58, 66,

70-71 of copending Application No. 11/913,828. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods recited in the '828 application encompass treating the claimed cancers (claim 49) with the claimed compound (claim 6).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614